UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/788,110	02/15/2001	Maurizio Zanetti	UCSD-07017	2849

7590 08/25/2004

MAHA A. HAMDAN
MEDLEN & CARROLL , LLP
101 HOWARD STREET, SUITE 350
SAN FRANCISCO ,, CA 94105

EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/788,110	ZANETTI, MAURIZIO	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *To 28, 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *9, 11-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *December 2, 2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Election filed June 28, 2004 in response to the Office Action of June 1, 2004 is acknowledged and has been entered. Claims 1-18 are pending in the application and Claims 9 and 11-18 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-8 and 10 are currently under prosecution.

2. The response to the restriction requirement of June 1, 2004 has been received. Applicant's election without traverse of Group I, claims 1-8 and 10 in the Paper filed June 28, 2004 is acknowledged.

Specification

3. The specification on page 1 should be amended to reflect the status of the provisional parent application,

For applicant's convenience, the appropriate form for claiming benefit to provisional application is as follows:

"This application claims benefit to provision application **********, filed **, now abandoned."

4. It does not appear that an Abstract of the Disclosure has been submitted since none is found in the file. If Applicant has submitted said Abstract, it would be appreciated if a copy of said Abstract is submitted in response to this action. If it has not already been submitted, the submission of an Abstract of the Disclosure is required.

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see in particular page 25, line 19. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC ' 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

7. Claims 1-8 and 10 are rejected under 35 USC 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the claimed invention.

The claims are drawn to a universal vaccine for treating tumors of any origin comprising at least one telomerase reverse transcriptase (hTRT) peptide in an amount effective for initiating and enhancing a cytotoxic T lymphocyte response against mammalian cancer cells and a physiologically acceptable carrier. The specification teaches that a method for treating tumors currently being evaluated makes use of telomerase, which normal body cells, other than sperm and the hematopoietic system, neither produce nor require. Attempts to develop a drug that will block the action of the enzyme sufficiently to either inhibit the growth of new tumor cells or cause the death of older ones have been made (page 5, lines 4-13). Despite the wide-ranging and expensive efforts expended in researching, developing and evaluating new treatments and cures for tumors and cancers, no truly significant advances or completely satisfactory treatments have thus far been achieved (p. 6, lines 15-18). Applicant demonstrates that the majority of normal individuals and patients with prostate cancer express precursor telomerase reverse transcriptase (TRT) cytotoxic T lymphocytes (CTL) and when these are immunized *in vitro*

against two HLA-A2.1 restricted peptides from hTRT develop hTRT specific CTL. This suggests the existence of precursor CTL for hTRT in the repertoire of normal individuals and cancer patients. Most importantly, cancer patients CTL specifically lysed a variety of HLA-A2+ cancer cell lines, demonstrating immunological recognition of endogenously-processed hTRT peptides. In addition, *in vivo* immunization of HLA-A2.1 transgenic mice generated a specific CTL response against both hTRT peptides. Thus, based on the induction of CTL responses *in vitro* and *in vivo* and the susceptibility to lysis of tumor cells of various origins by hTRT CTL, Applicant suggests that hTRT could serve as a universal cancer vaccine for humans (para bridging pages 10-11). It is reasonable that expression of hTRT in cancer cells is a likely source of peptides that, upon association with MHC Class 1 molecules, could target CTL to cancer cells and since high hTRT activity is widespread among human tumors, hTRT could serve as a universal tumor antigen for immunotherapy and vaccine approaches (para bridging pages 11-12). HTRT is encoded in the genome and is in all respects a self-antigen. Consequently, CD8+ T lymphocytes with a receptor for MHC/hTRT peptide complexes are expected to be eliminated during thymic negative selection, reducing the potential precursor T cell repertoire and imposing limitations on their expansion upon encounter with tumor cells in adult life. Additionally, stimulation by antigen in the absence of a second signal induces clonal anergy, further hampering the potential repertoire. The extent to which these events affect the normal adult repertoire and whether or not exposure to hTRT during cancer formation has any adverse effect on the ability of cancer patients to respond, is not known. Because answering these questions is relevant to future strategies of immune intervention targeted at hTRT, the ability of normal individuals and cancer patients to mount a CTL response *in vitro* against two hTRT

peptides restricted by the HLA-A2 allele was analyzed (p. 12, lines 6-17). The specification exemplifies *in vitro* immunization which leads to the production of hTRT specific CTL and the *in vivo* production of CTL against hTRT peptides in an animal model that does not have a tumor burden. The specification further teaches that hTRT peptides can expand precursor CTL in PBMC of both normal individuals and patients with prostate cancer and induce MHC Class I-restricted HLA-A2 restricted, peptide-specific CTL responses (para bridging pages 27-28) and further teaches that the available CTL repertoire for hTRT is preserved in normal individuals and in individuals with cancer which suggests that exposure to cancer does not cause deletion or anergy of clonotypes specific for hTRT (p. 28, lines 29-32). The specification states that the PMBC of three therapy resistant patients with metasteses responded to *in vitro* immunization with the exemplified peptides by developing hTRT CTL. It was surprising that the CTL could be induced at such an advanced stage of disease which is generally characterized by immunosuppression and given the above, it is expected that the two peptides identified in this study may be used for vaccination of HLA-A2+ cancer patients(para bridging pages 28-29). The specification further teaches that the future of hTRT-based vaccination will depend on the type of side effects that may follow immunization since the possibility exists that hTRT vaccination could result in autoimmunity and destruction of normal cells and further experimentation is needed to determine whether hTRT-based vaccination in cancer patients is safe or possible (para bridging pages 29-30).

One cannot extrapolate the teaching of the specification to the enablement of the claims because neither the *in vitro* nor the *in vivo* studies presented in the specification are commensurate in scope with the claimed invention which is drawn

to a universal vaccine for the treatment of cancer. Applicant is correct in the statement that despite the wide-ranging and expensive efforts expended in researching developing and evaluating new treatments and cures for tumors and cancers, no significant advances or completely satisfactory treatments have thus far been achieved. Although applicant demonstrates *in vitro* expansion of CTL and *in vivo* production of CTL in a mouse model, the specification provides no nexus between these experiments and the claimed universal cancer vaccine which is contemplated for use in humans because the *in vitro* expansion system does not provide an intact immune system, the peptides that are used to induce CTL are in contact with the lymphocytes for long periods of time and the target cells are incubated with the CTL for long periods of time, neither of which occur in the *in vivo* environment. Further, the *in vivo* experiments disclosed do not remedy the problems of the *in vitro* experiments because the model does not include animals with tumor load. Although applicant states that it is reasonable that expression of hTRT in cancer cells is a likely source of peptides that, upon association with MHC Class 1 molecules, could target CTL to cancer cells and since high hTRT activity is widespread among human tumors, hTRT could serve as a universal tumor antigen for immunotherapy and vaccine approaches, the specification also states that CD8+ T lymphocytes with a receptor for MHC/hTRT peptide complexes are expected to be eliminated during thymic negative selection, reducing the potential precursor T cell repertoire and imposing limitations on their expansion upon encounter with tumor cells in adult life. Additionally, stimulation by antigen in the absence of a second signal induces clonal anergy, further hampering the potential repertoire.

In agreement with the teachings of the specification, the unpredictability of cancer vaccines and in particular peptide vaccines that stimulate CTL are well

known in the art. For example, Kirkin et al, 1998, APMIS, 106 : 665-679 et al teach that in particular for tumor antigens (even with the existence of precursor CTL), due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract). Further, Chaux et al, Int J Cancer, 1998, 77: 538-542 teach some of the CTLs have an affinity that is too low for the recognition of cells that have processed the antigen, which is different from the *in vitro* conditions like those presented in the instant specification, in which the synthetic peptides are in high number when incubated with the cells (p.541, second column, second paragraph). Given the above, even if a peptide was recognized by T-cells *in vitro* from patients with cancer, it could not be predicted that the T-cells would recognize these peptides *in vivo* and if not recognized *in vivo*, it is clear that one would not know how to use the claimed peptides/universal vaccine. Similarly Sherman, LA et al, 1998, Critical reviews in Immunol, 18(1-2): 47-54 teach that self-tolerance may eliminate T cells that are capable of recognizing T-cell epitopes with high avidity . Smith RT, 1994, Clin Immunol, 41(4): 841-849, teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (again, even if precursor CTL exist in the system) (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limit the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specific antigen in the necessary MHC context (p.484). Given the above, one would not know how to use the claimed universal vaccine.

Further, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on

which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

In addition, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence, as set forth above, suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph). Thus based on the teaching in the art and in the specification, one cannot predict that an adequate *in vivo* T cell response useful for immunotherapy, as contemplated, could be induced by the peptides of the invention in patients having tumor burden as contemplated. In addition, as drawn to peptide tumor vaccines for the induction of a T-cell response, Kirkin et al, *Supra* review several melanoma-associated antigens,

including NY-ESO1, and conclude that initiation of a strong immune response *in vivo* is an extremely rare event (p.674, first column, last paragraph). Kirkin et al teach that for some antigens, due to the existence of self-tolerance, only T cells with low affinity T-cell receptors are produced (abstract). Kirkin et al teach that although several peptides of melanoma associated antigens have been identified as recognized by CTL *in vitro*, and peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response *in vivo*, only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (p.666, second column, second paragraph, last 6 lines). Further, even this peptide EVDPIGHLY of MAGE-A3 produces a very low level of CTL response which is detectable only by a very sensitive method, as taught by Chaux et al, Int J Cancer, 1998, 77: 538-542, abstract.

Finally, the specification raises the issue drawn to whether or not the claimed invention can in fact be used wherein it is stated that the future of hTRT-based vaccination will depend on the type of side effects that may follow immunization since the possibility exists that hTRT vaccination could result in autoimmunity and destruction of normal cells" and further experimentation is needed to determine whether hTRT-based vaccination in cancer patients is safe or possible. In the absence of objective evidence, it cannot be predicted from the information in the specification as to whether or not the claimed vaccine is either safe or possible to use as contemplated.

The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed universal vaccine would function as claimed or as contemplated with a reasonable expectation of success.

For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

8. If Applicant were able to overcome the rejection set forth above claims 1-8 and 59 with still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a universal vaccine for treating tumors of any origin comprising SEQ ID NOS: 1 and 2, wherein the patients treated express HLA-A2.1, does not reasonably provide enablement for a universal vaccine for treating tumors of any origin, comprising at least one telomerase reverse transcriptase peptide in an amount effective for initiating and enhancing a cytotoxic T lymphocyte (CTL) response against mammalian cancer cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a universal vaccine for treating tumors of any origin, comprising at least one telomerase reverse transcriptase peptide in an amount effective for initiating and enhancing a cytotoxic T lymphocyte (CTL) response against mammalian cancer cells. This means any telomerase reverse transcriptase peptide from any species since the telomerase is not defined in the specification. This also means a vaccine for treating tumors of any origin regardless of HLA expression in the patient.

The specification teaches that the cytotoxic activity of the CTL engendered by the peptides was dependent upon expression of the HLA-A2 molecule (page 23, lines 8-10). The specification further teaches that the HLA-A2 allele is expressed in about 50% of the Caucasian population (p. 23). Further the specification teaches that the exemplified peptides in fact down specifically to HLA-A2.1 (p. 25) and that not

all selected peptides were effective at generating *in vitro* killing of cancer cells and required modification in order to generate effective CTL (p. 27).

One cannot extrapolate the teaching of the specification, as drawn to Claims 1-8 and 59, to the scope of the claims because the specification has clearly taught the dependence of the vaccine on HLA-A2.1 expression and that this expression is not universal, therefore it is clear that the vaccine cannot be universal. Further, as drawn to claims 1, 5-8 and 59, the specification teaches that not all of the peptides tested were effective at generating CTL that would even function *in vitro* for the killing of cancer cells. Further, given the teaching of Kirken et al, *Supra*, one would not know how to use the broadly claimed invention. The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the claimed universal vaccine would function as claimed or as contemplated with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC ' 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. ' 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 1, 6, 8, 59 are rejected under 35 U.S.C. ' 102(b) as being anticipated by US Patent No. 6,093,809.

It is noted that the preamble recitation of a universal vaccine is merely suggestive of an intended use and is not given weight for purposes of comparing the claims with the prior art. The claims read on the active ingredients *per se*, which is a human telomerase reverse transcriptase peptide and a physiologically acceptable carrier, an adjuvant.

US Patent No. 6,093,809 teaches human telomerase reverse transcriptase (see abstract) and specifically teaches the production of antibodies to said human telomerase reverse transcriptase comprising immunizing various hosts by injection of the telomerase protein in combination with various adjuvants (col 30, lines 19-31).

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar, PhD
Primary Patent Examiner
August 23, 2004